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Original article

Lp-PLA2, a potential protector of lung cancer patients complicated with pleural effusion from lung diseases, proves effective for the diagnosis and pathological classification of lung cancer

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ABSTRACT

Abnormal lipid metabolism plays a crucial role in cancers, but few studies have investigated the relationship between lipoprotein-associated phospholipase A2 (Lp-PLA2) and lung cancer. In this study, 58 benign lung disease (LB) and 57 lung cancer (LC) patients complicated with pleural effusion (PE) were included, and their fasting serum and PE samples were collected. Results showed that serum Lp-PLA2 in the LC group was lower than that in the LB group, and other serum lipids were higher ($P < 0.05$). Tumor markers from serum and the PE samples of LC patients were higher than those in the LB group ($P < 0.05$). Serum prealbumin (PA) in LC patients was higher than that in the LB group, and serum C-reactive protein (CRP) and procalcitonin (PCT) were lower ($P < 0.05$). In the LC group, serum Lp-PLA2 concentration was positively correlated with serum triglyceride (TG), Lp (a), carbohydrate antigen 199 (CA199), nutritional markers, and Lp-PLA2 in PE and negatively correlated with serum high-density lipoprotein cholesterol (HDLC), Apolipoprotein A1 (APOA1), CRP, PCT, and alpha fetoprotein (AFP) and LDH in PE. The ROC curve showed that the cutoff level of serum Lp-PLA2 for diagnosing LC was 226.685 (U/L) (sensitivity: 0.632, specificity: 0.793), while the C-index of the nomogram model combined with serum Lp-PLA2, age, and gender was 0.750. In LC patients, the higher serum Lp-PLA2 indicated higher probability of adenocarcinoma and lower probability of squamous cell carcinoma (SCC). In conclusion, Lp-PLA2 may be a protective factor of lung cancer among lung disease patients complicated with pleural effusion, and it would facilitate the diagnosis and pathological classification of lung cancer.

Introduction

It is well recognized that diet and obesity are risk factors for cancer [1,2] and that abnormal serum lipid levels and dyslipidemia are associated with a variety of cancers [3,4]. A meta-analysis showed a negative correlation between HDL-C and cancer. For every 10 mg/dL increase in HDL-C, the risk of cancer was reduced by 36% [5]. A Chinese prospective cohort study showed that high TC, LDL-C and non-HDL-C levels were negatively correlated with cancer [6]. However, the relationship between lipids and cancer remains controversial. The incidence rate of cancer varies with different types of tumor. Some studies have shown that lipids are associated with the occurrence and mortality due to tumors, while others showed opposite results [7].

Lung cancer is still the most common cause of death from cancer worldwide. In 2018, there were more than 230,000 new cases in the United States alone [8]. Although several studies have shown that liposomes were abnormal in lung cancer, the underlying mechanism is still obscure. It remains to be investigated whether liposomes can be used in the early diagnosis and classification of lung cancer [9].

Lipoprotein-associated phospholipase A2 (Lp-PLA2) belongs to group VII of the PLA2 superfamily. It is mainly secreted by macrophages and circulates in the blood in the form of LDLC and HDLC complexes. Lp-PLA2 was initially named as plasma platelet-activating factor acetylhydrolase (pPAF-AH) due to its hydrolysis of platelet-activating factor (PAF). In addition, Lp-PLA2 could hydrolyze oxidized-LDL into two bioactive products, which target endothelial cells (ECs), monocytes/macrophages, T cells, and neutrophils, inducing oxidative stress and immune response. Studies have shown that elevated serum LpPLA2 activity is independently associated with the incidence rate of abdominal aortic aneurysm (AAA) [10], and the serum LpPLA2 concentration was positively correlated with all-cause mortality in patients with coronary heart disease [11]. In addition, high LpPLA2 expression was associated with various tumors, such as prostate cancer and breast cancer,

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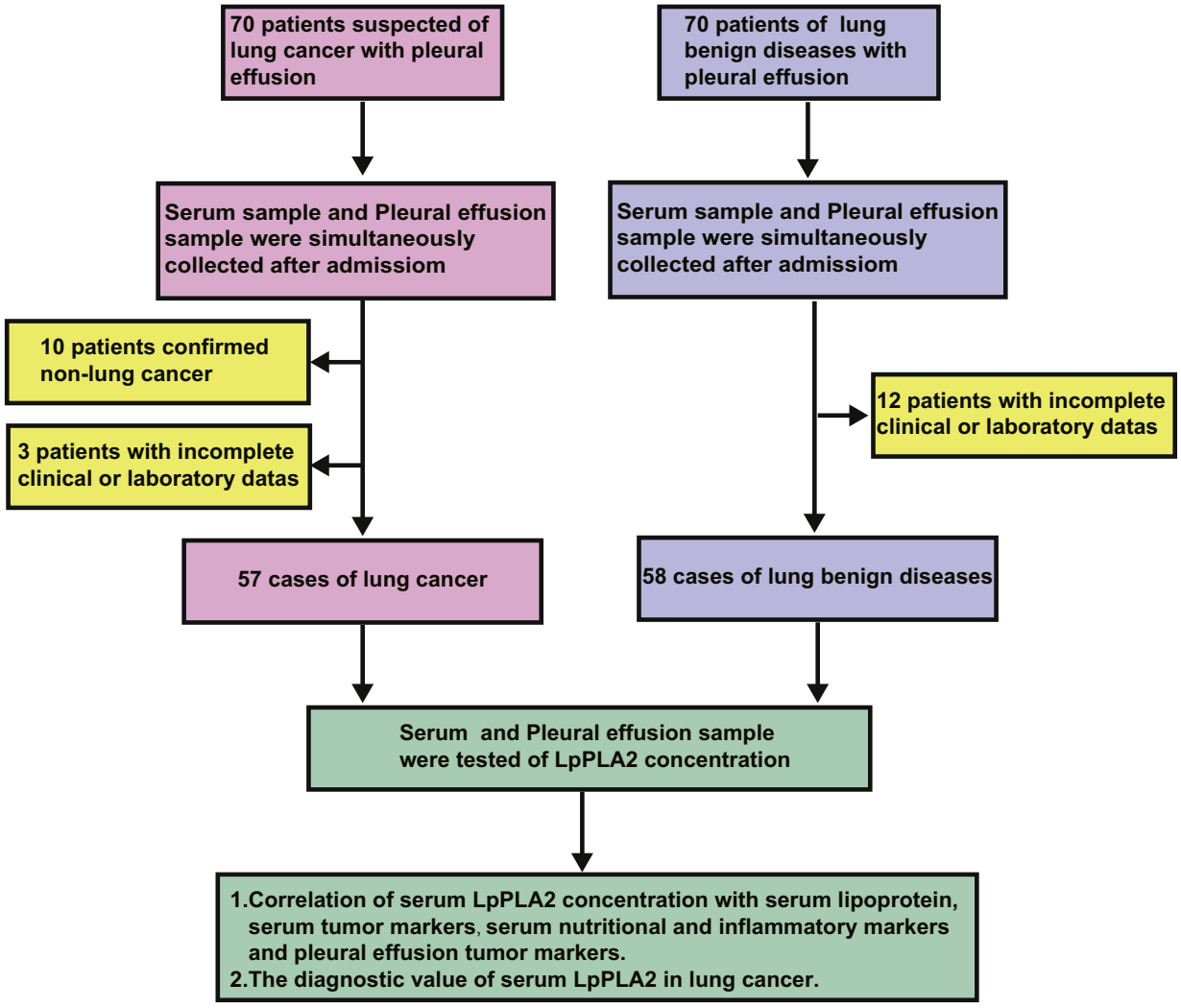

Fig. 1. Flow of the benign lung cohort and lung cancer cohort.

especially in metastatic and aggressive ones [12]. However, few studies have investigated the relationship between Lp-PLA2 and lung cancer.

In this study, we collected serum and pleural effusion samples from patients with benign lung diseases and lung cancer to compare the respective concentrations of Lp-PLA2 in both sets. We then discussed the value of using serum Lp-PLA2 concentration in diagnosing patients with pleural effusion for lung cancer, and its role in the pathological classification and tumor-node-metastasis (TNM) staging of lung cancer patients.

2. Materials and methods

2.1. Patient samples

Our research subjects were 70 suspected lung cancer patients and 70 benign lung disease patients, all with pleural effusion. We collected their fasting serum samples and pleural effusion samples on the second day after their admission into hospital. Those who met the following criteria were excluded from the research: (1) suspected patients were confirmed to be free of lung cancer and (2) patients lacked complete clinical and laboratory data. Finally, 57 cases of lung cancer patients and 58 cases of benign lung disease patients were included (Fig. 1). Serum and pleural effusion Lp-PLA2 concentration, tumor markers, and serum lipids were tested.

2.2. Diagnosis criteria and TNM staging criteria

Diagnosis criteria: Suspected lung cancer patients were diagnosed according to the clinical manifestations, chest CT scans, and histopathological examination. Confirmed lung cancer patients were classified into small cell lung cancer (SCLC), squamous cell carcinoma (SCC), adenocarcinoma, and other types of non-small cell lung cancer (NSCLC) [13].

TNM staging criteria: The eighth edition of the TNM classification was used for lung cancer staging [8].

2.3. Biological detection

Serum and pleural effusion Lp-PLA2 concentration, serum lipids, serum nutritional markers, and C-reactive protein (CRP) were tested by ARCHITECT C16000 (Abbott, USA); serum and pleural effusion tumor markers were detected by ARCHITECT i2000 (Abbott, USA); and serum procalcitonin (PCT) levels was determined by Roche Cobas e411 electrochemiluminescence analyzer (Basel, Switzerland).

2.4. Methods

First, the serum Lp-PLA2 and other laboratory indexes were compared among patients with benign lung diseases and lung cancer, and the correlation between serum Lp-PLA2 and serum lipids, tumor markers, serum inflammatory, and nutritional markers was determined. Sec-

Table 1
Biological and clinical information of the cohorts.

	Benign lung diseases n1=58	Lung cancer n2=57	P
Biological information			
Age (years)	66.4 ±16.9	64.9 ± 10.2	0.254
Gender, n (%)			0.102
Male	42 (72.4)	33 (57.9)	
Female	16 (27.6)	24 (42.1)	
Lung cancer new diagnosis, n (%)			
Yes	-	41 (71.9)	
No	-	16 (28.1)	
Type of lung cancer, n (%)			
Adenocarcinoma	-	31 (54.4)	
Squamous cell carcinoma	-	9 (15.8)	
Other types of NSCLC	-	13(22.8)	
Small cell carcinoma	-	4 (7)	
Primary or metastatic lung cancer, n (%)			
Primary lung cancer	-	52 (91.2)	
Metastatic lung cancer	-	5 (8.8)	
TNM grade, n (%)			
I+II	-	9 (15.8)	
III+IV	-	48(84.2)	

ond, the value of serum Lp-PLA2 in diagnosing lung cancer was determined. Third, its significance in lung cancer pathological classification and TNM staging for patients was analyzed.

2.5. Statistical analysis

All the graphs and the corresponding statistical analyses were performed using R (Version: 4.0.2). Continuous variables were expressed as mean ±SD, and t test was used for comparisons between groups. Categorical variables were expressed as numbers (percentage), and comparisons between groups were performed using Chi-square. The correlations between serum Lp-PLA2 and other indicators were assessed by Spearman's correlation analysis. Receiver operating curve (ROC) and nomogram were used to determine the role of serum Lp-PLA2 in the diagnosis, pathological classification, and staging of lung cancer. P ≤0.05 was considered to indicate statistical significance.

3. Results

3.1. Basic information of the study cohort

In our cohort, no significant difference in age and gender was observed between the benign lung diseases group and the lung cancer group (P > 0.05). A total of 71.9% of patients in the latter group were newly diagnosed, while the remaining were hospitalized patients for radiotherapy and chemotherapy. Among all lung cancer patients, those who suffered from adenocarcinoma accounted for 54.4%, squamous cell carcinoma 15.8%, other types of non-small cell lung cancer (NSCLC) 22.8%, and small cell lung cancer (SCLC) 7%. Most of them were primary lung cancer patients (91.2%), whose TNM grade was mostly stage III and IV (84.2%) (Table 1).

3.2. Comparison of laboratory indicators between the two groups

Among lipoprotein indicators, total serum cholesterol (CH), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), apolipoprotein A1 (APOA1), apolipoprotein B (APOB) and lipoprotein (a) (LP (a)) in the lung cancer group were higher than those in the benign lung disease group, while serum Lp-PLA2 concentration was lower than that in the control group ($P < 0.05$). In addition, the levels of serum triglyceride (TG) and Lp-PLA2 in pleural effusion showed no significant difference between the two groups.

Among tumor markers, serum carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCCA) and lactate dehydrogenase (LDH) from the serum sample, and CEA, carbohydrate antigen 125 (CA125) and LDH from the pleural effusion sample in lung cancer patients were higher than those in the control group ($P < 0.05$), while serum CA125 concentration showed no significant difference.

For nutritional and inflammatory markers, serum prealbumin (PA) concentration in lung cancer patients were higher than that in the control group, and serum C-reactive protein (CRP) and procalcitonin (PCT) concentration were lower, while serum concentrations of total protein (TP), albumin (Alb), globulin (Glb) and albumin globulin ratio (AG) showed no significant difference (Fig. 2).

There was no significant difference in serum Lp-PLA2 concentration between the newly diagnosed and non-newly diagnosed lung cancer patients ($P > 0.05$) (Fig. 3).

3.3. Correlation between serum Lp-PLA2 concentration and lipoprotein, tumor markers, nutritional and inflammatory markers in the lung cancer group

For lipid-related parameters, the serum Lp-PLA2 concentration was negatively correlated with TG and Lp (a), but not correlated with HDLC and APOA1 in the control group, while in the lung cancer group, serum Lp-PLA2 concentration was positively correlated with TG and Lp (a), negatively correlated with HDLC and APOA1, but not remarkably correlated with LDLC. For tumor markers, serum Lp-PLA2 was positively correlated with serum carbohydrate antigen 199 (CA 199) and pleural effusion Lp-PLA2 in the lung cancer group and negatively correlated with alpha fetoprotein (AFP) and LDH with pleural effusion. Although serum Lp-PLA2 in the control group was negatively correlated with serum CA 199 and Lp-PLA2 in pleural effusion and positively correlated with pleural effusion AFP, no marked correlation was found between serum Lp-PLA2, serum CA 199, and pleural effusion Lp-PLA2. For inflammatory and nutritional markers, the serum Lp-PLA2 concentration was negatively correlated with CRP and PCT, while opposite results were observed in the control group. Serum Lp-PLA2 was weak positively correlated with TP, Alb, AG and PA in the lung cancer group, and no marked correlation was found between serum Lp-PLA2 and serum Glb. In the control group, serum Lp-PLA2 concentration was positively correlated with Alb and AG and negatively correlated with TP, Glb, and PA (Fig. 4).

3.4. The value of serum Lp-PLA2 in the diagnosis and pathological classification of lung cancer

The ROC curve showed that the cutoff value of serum Lp-PLA2 in the diagnosis of lung cancer was 226.685 (U/L), the sensitivity was 0.632, and the specificity was 0.793. Nomogram showed that the combination of serum Lp-PLA2, age, and sex was a better predictor in the diagnosis of lung cancer.

Cut-off values of serum Lp-PLA2 for the differentiation of lung squamous cell carcinoma (SCC) and adenocarcinoma were 213.050 (U/L) and 205.150(U/L), respectively. But the diagnostic efficiency was low, and the combination of serum Lp-PLA2, age, and sex had a higher diagnostic efficiency than serum Lp-PLA2 alone. The nomogram model showed the combination of serum Lp-PLA2, age and sex was better in identifying SCC and adenocarcinoma. It showed that among lung cancer patients, the higher concentration of serum Lp-PLA2 led to lower probability of developing SCC, but higher probability of developing adenocarcinoma (Fig. 5).

3.5. The value of serum Lp-PLA2 in TNM staging of lung cancer

There was no significant difference in serum Lp-PLA2 concentration between patients in TNM stage I-II and III-IV (Fig. 6).

Discussion

Lp-PLA2 mediates vascular inflammation by regulating lipid metabolism in the blood. It mainly exists in blood circulation by binding

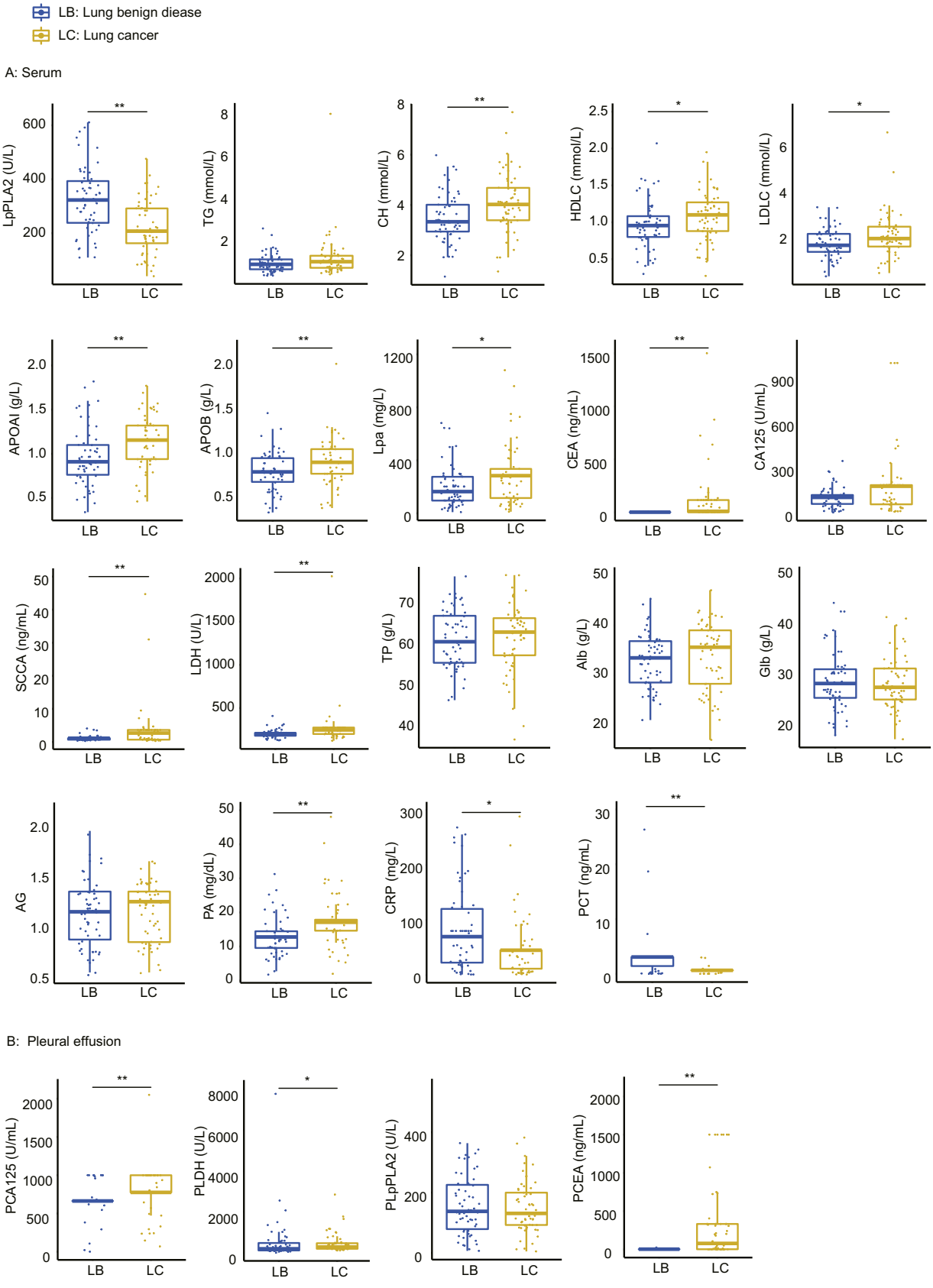

Fig. 2. Comparison of serum and pleural fluid lipids and tumor markers between benign lung disease patients and lung cancer patients.
*:$P<0.05$, **:$P<0.01$

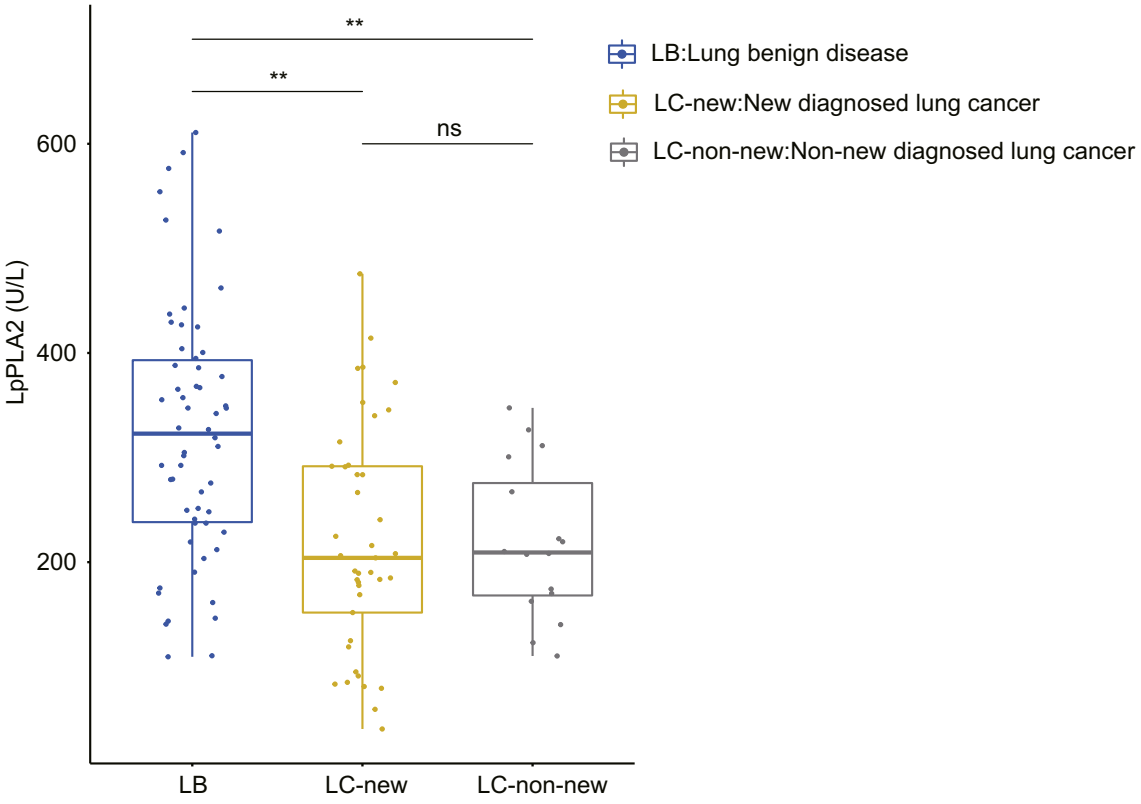

Fig. 3. Comparison of serum Lp-PLA2 concentration among benign lung disease patients, newly diagnosed, and non-newly diagnosed lung cancer patients. **:$P<0.01$, ns: no statistical difference.

with low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Interestingly, Lp-PLA2 can be transferred between LDL and HDL. Lp-PLA2, if bound with HDL, can resist atherosclerosis, but when bound with LDL, the enzyme produces the opposite effect [14]. Studies have shown different metabolic behaviors between LDL particles carrying Lp-PLA2 and LDL particles lacking Lp-PLA2 [15,16].

At present, the role of Lp-PLA2 in vascular inflammation and other related diseases (mainly atherosclerosis) has been widely studied [15]. In addition, the relationship between Lp-PLA2 and various cancers has also been increasingly investigated. Studies have shown that Lp-PLA2 may be a valuable biomarker or therapeutic target for prostate cancer, especially for ERG-positive prostate cancer [17]. Lp-PLA2 plays a causal relationship in the occurrence of colon cancer; therefore, the inhibition of Lp-PLA2 may be a promising method for the treatment of intestinal cancer [18]. Some studies have revealed a high expression of PLA2G in colon cancer, renal cell carcinoma, liver cancer and lung cancer, and high Lp-PLA2 protein and gene expression were significantly associated with poor prognosis of lymph node metastasis [12]. However, in addition to its oncogenic effect, Lp-PLA2 may play a beneficial role in some cancers such as melanoma, multiple myeloma, and glioblastoma [14]. Therefore, because of the complex tumor microenvironment, Lp-PLA2 exerted different effects on tumors due to the tumor types and stages. This study collected serum and pleural effusion samples from patients with benign lung diseases and lung cancer to compare the expression of Lp-PLA2 in the two groups and to explore the value of applying serum Lp-PLA2 in the diagnosis, pathological classification, and TNM staging of lung cancer.

In comparing the two groups, we found that most of the blood lipid indexes of lung cancer patients, including total serum cholesterol, HDLC, LDLC, APOA1, APOB and Lp (a), were higher than those in the control group, while the serum Lp-PLA2 concentration was lower. We observed the study cohort focusing on this abnormal lipoprotein and found no statistical difference in age and gender between the groups. However, 28.1% of patients were not newly diagnosed. This means they may have received surgery, radiotherapy and chemotherapy before hospitalization. To determine the effect of diagnosis and treatment of lung cancer patients on serum Lp-PLA2 concentration, we divided the patients into a newly diagnosed group and a non-newly diagnosed group, and found no significant difference in serum Lp-PLA2 concentration between them. Their Lp-PLA2 concentration levels were lower than those in the control group. Therefore, it can be speculated that the treatment process had little effect on the serum Lp-PLA2 concentration of lung cancer patients.

In analyzing the correlation between the serum Lp-PLA2 concentration and lipoprotein in patients with lung cancer, we found that serum Lp-PLA2 was positively correlated with TG and lipoprotein (a) (Lp (a)) and negatively correlated with HDLC and APOA1, but not significantly correlated with LDLC. It has been shown that a low concentration of Lp-PLA2 could bind to Lp (a). In individuals with elevated Lp (a), the affinity of Lp-PLA2 to Lp (a) was higher than that to LDLC [16,19]. The reference range of serum Lp-PLA2 concentration provided by the manufacturer was ≤ 670 U / L, and the average serum Lp-PLA2 concentration of lung cancer patients in this study was about 200 U/L, which is a relatively low benchmark. Therefore, serum Lp-PLA2 of lung cancer patients was mainly combined with Lp (a). However, there was no significant difference in the pleural effusion Lp-PLA2 concentration between the two groups, which may be relevant to the secretion manner of Lp-PLA2.

In the correlation analysis of serum Lp-PLA2 concentration and tumor markers in lung cancer patients, we found that the relationship in the cancer group was contrary to that in the control group. Tumor markers were generally recognized as laboratory indexes reflecting tumor classification and staging [20,21]; thus, it can be inferred that there were subtle changes and unique role of Lp-PLA2 in the occurrence and development of lung cancer. Therefore, the role of serum Lp-PLA2 in the diagnosis, pathological classification and TNM staging of lung cancer is worth further exploring.

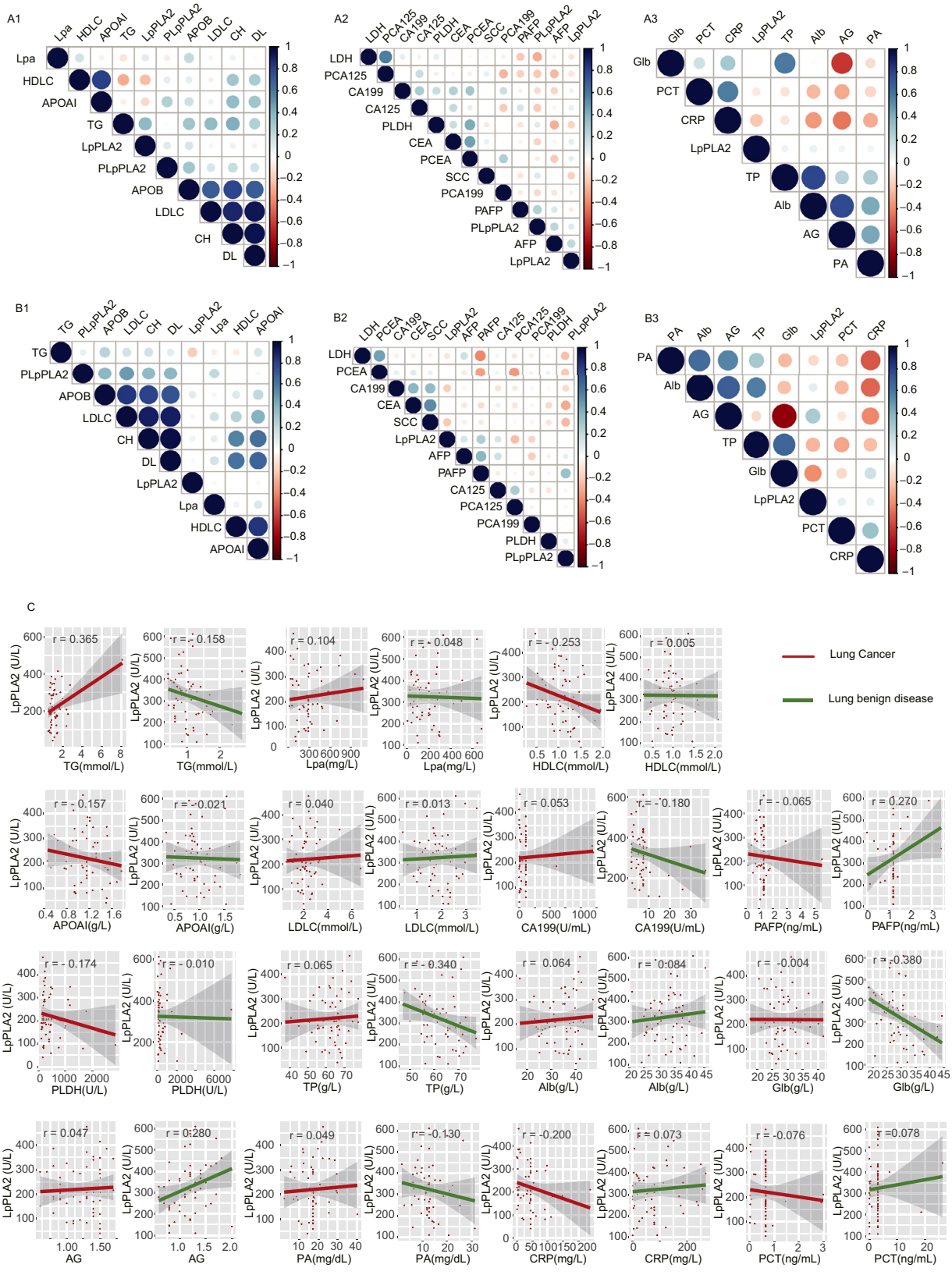

Fig. 4. Correlation of serum Lp-PLA2 with blood lipids, tumor markers, nutritional markers and inflammatory markers in benign lung disease patients and lung cancer patients.

A1. Correlation of serum Lp-PLA2 with blood lipids in lung cancer patients. A2. Correlation of serum Lp-PLA2 with tumor makers in lung cancer patients. A3. Correlation of serum Lp-PLA2 with nutritional markers and inflammatory markers in lung cancer patients. B1. Correlation of serum Lp-PLA2 with blood lipid in benign lung disease patients. B2. Correlation of serum Lp-PLA2 with tumor makers in benign lung disease patients. B3. Correlation of serum Lp-PLA2 with nutritional markers and inflammatory markers in benign lung disease patients. The intensity of correlation was expressed in different colors. The darker the blue, the stronger the positive correlation. The deeper the red color, the stronger the negative correlation. C. Comparison of the correlation of serum Lp-PLA2, blood lipid, tumor markers, nutritional markers and inflammatory markers between lung cancer group and benign lung disease group.

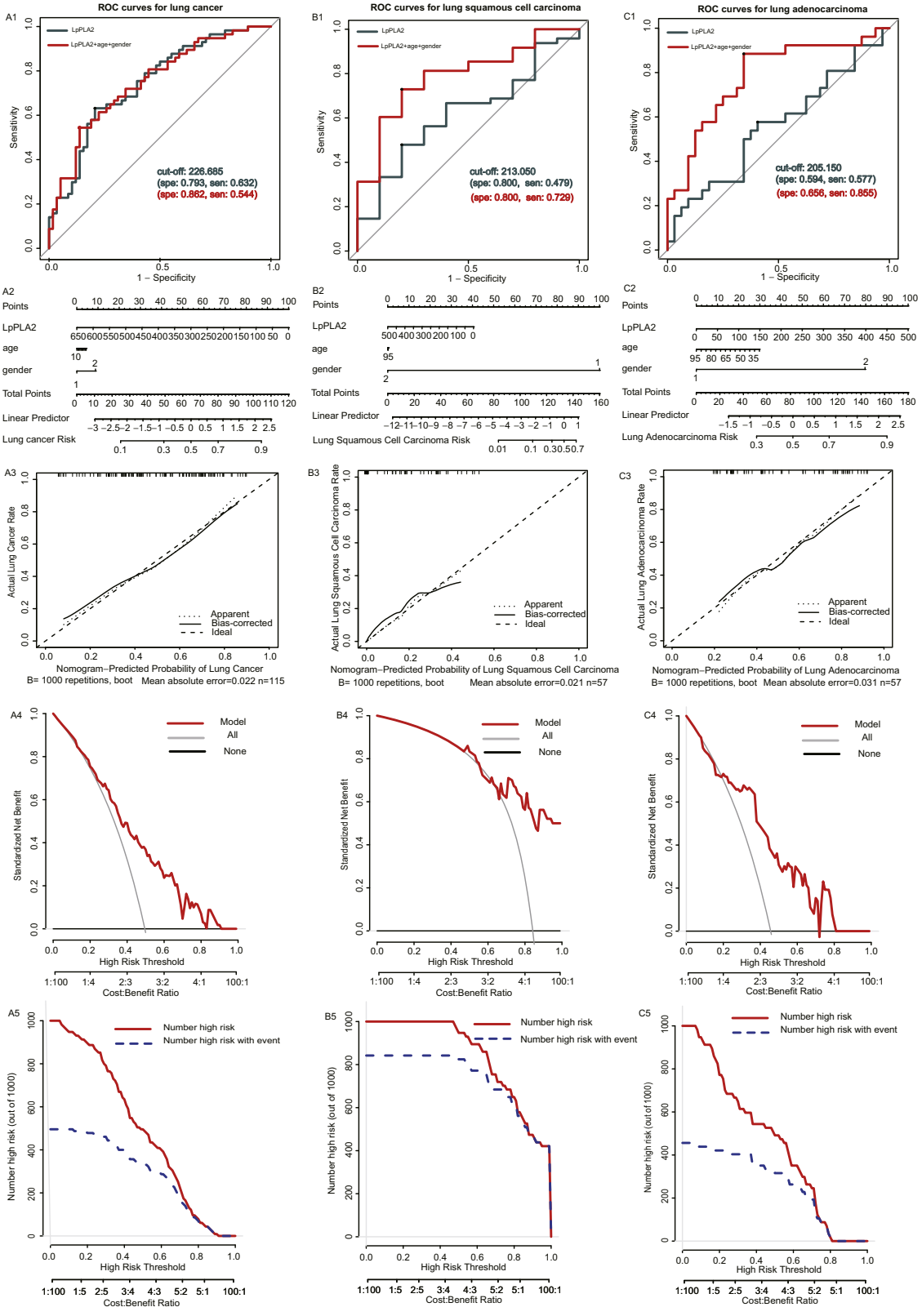

Fig. 5. ROC curves and nomogram models of serum Lp-PLA2 for diagnosis and pathological classification in lung cancer patients with pleural effusion. A. ROC curves and nomogram model of serum Lp-PLA2 for lung cancer diagnosis among lung diseases patients with pleural effusion. B. ROC curves and nomogram model of serum Lp-PLA2 for lung squamous cell carcinoma diagnosis among lung cancer patients with pleural effusion. C. ROC curves and nomogram model of serum Lp-PLA2 for lung adenocarcinoma diagnosis among lung cancer patients with pleural effusion.
1. ROC curves. 2: Nomogram. 3: Calibration curve. 4. Clinical decision curve. 5. Clinical impact curve.
spe: specificity, sen: sensitivity
gender: 1: male; 2: female

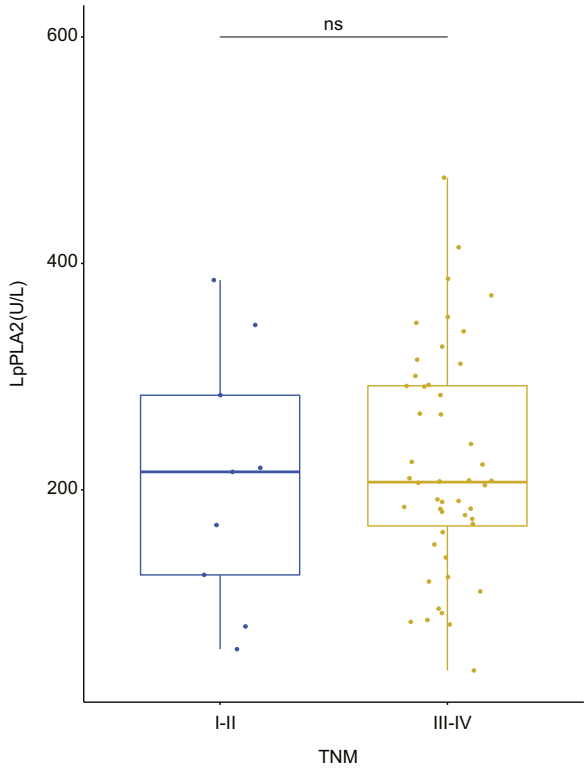

Fig. 6. Comparison of serum Lp-PLA2 concentration among different TNM stages of lung cancer.
ns: no statistical difference.

When analyzing the correlation between serum Lp-PLA2 concentration and inflammatory or nutritional markers, we found that serum Lp-PLA2 concentration had a weak positive correlation with most nutritional makers, and it was negatively correlated with CRP and PCT in lung cancer patients. Some studies have suggested that the inflammatory and immunosuppressive agents released by inflammatory cells could not only promote tumor proliferation, angiogenesis, invasion and metastasis but also inhibit the host immune system and accelerate the growth and development of tumor [22]. In addition, some scholars have revealed an active inflammatory reaction in neurofibroma and showed that preventing inflammation in the observed tumor site was an approach to treat neurofibroma [23]. More importantly, it has been proved that the existence and degree of chronic systemic inflammatory response may lead to the decline of progressive nutrition. A special nutritional intervention could decrease the inflammatory state and improve the nutritional status, which was a successful strategy for the treatment of colorectal cancer [24]. Therefore, it can be speculated that low serum Lp-PLA2 in lung cancer patients may be related to high inflammatory state and the progressive nutritional decline caused by it.

We further studied the value of serum Lp-PLA2 concentration in the diagnosis and pathological classification of lung cancer. It is known that the pathological type of lung cancer was related to gender and age [25]; hence, we drew two ROC curves of serum Lp-PLA2 alone and its combination with age and gender to compare the diagnostic efficacy. We found that serum Lp-PLA2 alone could be used for the diagnosis of lung cancer in patients with lung disease accompanied by pleural effusion, but the combined diagnosis could improve the specificity. However, serum Lp-PLA2 alone was not effective enough in the differential diagnosis of lung squamous cell carcinoma and adenocarcinoma. Therefore, we further established a diagnostic model combined with serum Lp-PLA2, age and gender by using nomogram.

Nomogram is based on multifactor regression analysis by using multiple clinical indicators or biological attributes, combined with line segments with high or low scores. Based on the total scores of multiple variables, we could predict a certain clinical outcome or the probability of certain events. In recent years, nomogram has seen growing application in tumor diagnosis and prognosis prediction. Its visual output enabled clinicians to use clinical indicators more intuitively for the diagnosis and treatment of diseases [26,27].

Through our nomogram model, we found that serum Lp-PLA2 concentration can be used to diagnose lung cancer patients with a C-index of 0.750. In addition, for the pathological types of lung cancer patients, Lp-PLA2 had a high differential value. Patients with high serum Lp-PLA2 were more likely to develop adenocarcinoma (C-index=0.777), while those with lower Lp-PLA2 had a high probability of developing squamous cell carcinoma (C-index=0.843). To our knowledge, our study was the first to investigate the diagnosis and pathological types of lung cancer aided by differential value of serum Lp-PLA2 concentration.

However, there was no significant difference in serum Lp-PLA2 concentration among lung cancer patients with different TNM stages. Therefore, we believe that serum Lp-PLA2 concentration could guide the identification of lung cancer in patients with lung diseases and the pathological classification of lung cancer, but it could not distinguish the TNM staging.

There are some limitations in this study. First, we recruited only patients with pleural effusion, which resulted in a small number of cases, and some lung cancer patients were not newly diagnosed, which may cause a certain bias in research results. Second, Lp-PLA2 gene polymorphism was confirmed to be related to the disease [28,29], yet the genotypes were not detected in this study. Third, the relationship between serum Lp-PLA2 concentration and mortality of lung cancer patients was not discussed.

In conclusion, serum Lp-PLA2 concentration had certain value for diagnosing lung cancer patients with pleural effusion and could guide the pathological classification of lung cancer. Prospective studies based on large samples should be carried out in future to further explore the diagnostic and prognostic value of serum Lp-PLA2 in lung cancer patients and provide a new laboratory basis for the diagnosis and treatment of lung cancer.

Ethics approval: Data collection and analysis of the cases in this study were approved by the Medical Ethics Committee of Taizhou hospital of Zhejiang Province. (Ethical approval code: K20180741)

Consent for publication: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Authors' contributions

Jing Wang: Definition, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing-Original Draft, Writing-Review & Editing, Visualization, Project administration, Funding acquisition; **Minya Jin:** Definition, Methodology, Investigation, Resources, Data Curation; **Yijun Chen:** Formal analysis, Data Curation, writing; **Yuan Yuan:** Definition, Investigation; **Yi Ruan:** Definition, Methodology, Resources, Data Curation, Supervision, Project administration; **Guoguang Lu:** Definition, Methodology, Investigation, Resources, Data Curation, writing-Original Draft, Writing-Review & Editing, Supervision, Project administration.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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